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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/896,053	07/17/97	JANSSENS	S 0609.4280001
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EXAMINER

BECKERLEG, A

ART UNIT

PAPER NUMBER

1632

DATE MAILED:

01/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/896,053

Applicant(s)

JANSSENS ET AL.

Examiner

Anne Marie S. Beckerleg

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 July 2000.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 21.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

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Continued Prosecution Application

The request filed on 7/27/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/896,053 is acceptable and a CPA has been established. Applicant's after final amendment received on 12/27/99 and applicant's amendment and declaration received on 9/12/00 have been entered. Claims 1-21 have been canceled and new claims 22-41 have been entered. Claims 22-41 are pending and active in the instant application. An action on the CPA follows.

The text of those sections of Title 35, US Code, not included in the instant action can be found in previous office actions.

The objection to the oath or declaration is maintained. The examiner acknowledges the applicant's previously stated intent to correct the defects in the declaration until such time that allowable subject matter has been indicated.

Claim Rejections - 35 USC § 112

The rejection of claims 1-21 under 35 U.S.C. 112, first paragraph, is maintained in part over new claims 22-41. Applicant's arguments and the declaration by inventor Stefan Janssens has

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been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons or record as discussed in detail below.

In view of applicant's arguments and the declaratory statements of Stefan Janssens, the scope of enablement has been modified. The modifications are underlined below for clarity. The specification, while being enabling for a method of inducing vasodilation in a mammal comprising: introducing into the lungs of a mammalian patient in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type nitric oxide synthase gene operably linked to a strong viral promoter, wherein the introduction of said gene into the lungs of said patient results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, and a method of treating hypoxic pulmonary hypertension in mammals comprising introducing into the lungs of said mammal in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type nitric oxide synthase gene operably linked to a strong viral promoter, wherein the introduction of said gene into the lungs of said mammal results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, does not reasonably provide enablement for a method of treating any and all forms of primary or secondary hypertension in all mammals comprising introducing by any route of delivery, any vector encoding any nitric oxide synthase gene under the control of any promoter.

In regards to identifying and using NOS mutants in the instant invention, the applicant's representative and the declaratory statements of Stefan Janssens argue that the prior art provides sufficient guidance for making mutants of NOS which retain wild type functionality. In support of

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this argument, the applicant has submitted a number of prior art references. These references provide information about specific residues or regions in various species and isoforms of NOS which affect various aspects of NOS activity. The applicant states that with this body of information, the skilled artisan would be advised as to which residues and regions to avoid mutating and as such undue experimentation would not be required to make NOS mutants with wild type activity. However, the prior art references serve to demonstrate that the NOS molecules are complex and that numerous residues are important to functionality. Further, as discussed in the previous office action, even mutating residues which are not critical for a particular functionality can have profound effects on protein folding, half-life, and pH and temperature sensitivity. The specification does not disclose a single mutant NOS molecule which retains wild type NOS activity. Further, the two ceNOS mutants reported by Chen et al. (document AT30) and alleged by the applicant to represent NOS mutants suitable for use in the instant invention have significantly reduced enzymatic activity compared to wild type NOS (Chen et al., page 25064, Figure 2). It is also noted that the Chen et al. paper does not report on the half-life or stability of the mutated NOS. Furthermore, the Federal Circuit has stated that:

a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to

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the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997).

Therefore, in view of the complexity of the NOS molecule as evidenced by the number of mutations which result in loss of enzymatic activity, the further effects of mutations on protein folding, half-life, and pH and temperature sensitivity, the lack of guidance provided by the specification for residues and regions in which mutations will not affect functionality or wild type NOS properties, and the lack of teachings in the prior art and the specification of any NOS mutant that retains wild type functionality, it would have required undue experimentation to determine which NOS mutants would be useful for the instant methodologies.

The applicant argues that the applicant's need not teach now to make and use every embodiment within a claim citing *In re Fisher*. However, it is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). The applicant's claims read broadly on the administration of any vector encoding NOS by any route of administration. Numerous vectors were reported in the art at the time of filing with significantly different properties and functions including differences in cell tropism, the ability to integrate into the host chromosome, the ability to generate host immune responses, the ability to replicate, and the ability to be maintained in the cell over periods of time. Of the numerous

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vectors known in the art, the specification has provided an enabling disclosure for the use of adenoviral vectors.

The applicant's representative and the declaratory statements of Stefan Janssens argue that vectors other than adenoviral vectors had been used successfully to express genes in lung tissue prior to the date of filing of the instant application. The applicants further argue that the prior art also supports the transfection/transduction of lung tissue by routes of administration other than the delivery of aerosolized vector to the lung. In support of these arguments, the applicants have provided several references. The relevance of these references to enablement of the instant invention is discussed below. Naldini et al. discloses retroviral HIV based vectors which are demonstrated to transduce fibroblasts *in vitro* and neurons *in vivo*. The *in vivo* data however involves the intracranial administration of the vector encoding a marker protein. A nexus cannot be drawn between the data of Naldini and the applicant's invention since unlike the lungs, the brain is an immune privileged organ, and the Naldini data does not demonstrate that the observed level of neuron transfection or the level of marker gene expression from the HIV vector correlates with the level of gene expression necessary in lungs to have any therapeutic effect on any symptom associated with hypertension. Neither Flotte et al. nor Kreuzer et al. provide any *in vivo* data. Flotte et al. discloses an AAV vector which can transduce airway epithelia cells *in vitro*. Kreuzer et al. discloses the transfection of primary arterial cells *in vitro* with a specialized adenoviral liposome combination. However, neither reference correlates the *in vitro* levels of gene expression with a therapeutic level of airway transfection and gene expression *in vivo*. Muller et

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al. teaches the transfection of lung tissue by percutaneous right heart catheterization with liposome/plasmid or with adenovirus encoding a marker protein. Nabel et al. discloses that DNA liposomes can be safely administered to humans by percutaneous catheter gene delivery. Again, no correlation is made in either reference between the level of lung cells transfected, the level of gene expression, and any therapeutic effect on any disease symptom. In fact the review of gene transfer and vascular disease submitted by the applicants as exhibit P clearly points out the problems associated with current gene transfer vectors. Nabel et al. disclose that low transduction efficiency limits the usefulness of cationic liposome vectors and retroviruses in vascular tissue (Nabel et al., exhibit P, page 448-449). Nabel et al. also makes the point that while the literature at the time of filing reports the feasibility of direct gene transfer into lung tissue, it is currently unknown whether these levels of expression are sufficient for potential vascular therapies in view of the following factor, " .. pathophysiology, the local vascular disorder, the rate of synthesis and half life of a recombinant protein, autocrine or paracrine effects of the recombinant protein, and other factors" (Nabel, page 450-451, see especially page 450, column 2, paragraph 2, and page 451, column 1, paragraph 4). Thus, Nabel et al. in reviewing the state of the art of gene transfer in relation to vascular disease at the time of filing supports the unpredictability of achieving therapeutic levels of gene expression using any currently available gene transfer vectors as taught by Verma et al. and Orkin et al., cited in previous office actions. Further, in regards to routes of administration other than aerosolized delivery of the adenovirus encoding NOS to the lung, it is noted that the same factors which Nabel identifies as affecting the use of different vectors to

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achieve therapeutic gene expression apply to the use of different routes of vector administration, as the site of gene delivery will significantly affect the amount of vector that reaches the target tissue and thus the amount of cell transfection and the level of therapeutic gene expression in the target disease tissue. Therefore, while the references provided support the ability to express a foreign gene in vascular tissue using vectors other than adenovirus, the prior art references do not teach or demonstrate the level of lung epithelial or vascular cell transfection and the level of gene expression of a potentially therapeutic gene such as NOS that correlates with the treatment of any symptoms associated with any vascular disease. Further, based on the art recognized factors associated with therapeutic gene expression as discussed by Nabel et al., Verma et al., and Orkin et al., the skilled artisan would not be able to predict without undue experimentation whether the delivery of adenoviral vectors or any other vector encoding NOS by routes other than the aerosol delivery to the lung would result in a level of cell transfection and gene expression that would correlate with any therapeutic effect on the diseased vascular tissue.

The applicant argues that the rat model is an excepted model for pulmonary hypertension in humans. Applicant's arguments have been accepted in part. As stated above, the scope of enablement has been modified to recite that the specification is enabling for a method of treating hypoxic pulmonary hypertension in mammals comprising introducing into the lungs of said mammal in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type nitric oxide synthase gene operably linked to a strong viral promoter, wherein the introduction of said gene into the lungs of said mammal results in pulmonary vasodilation that

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does not significantly affect systemic blood pressure or cardiac index. However, the specification still fails to provide enablement for the treatment of any forms of pulmonary hypertension. As discussed in detail in previous office actions, primary pulmonary hypertension is a rare and difficult to diagnose disorder. According to Giuseppe Pietra, plexogenic pulmonary arteriopathy (PPA), characterized variably by concentric laminar intimal fibrosis, plexiform lesions, and necrotizing arteritis, is the most common form of arteriopathy in primary pulmonary hypertension (Pietra (1994) Chest, Vol. 105 (2 supp.), page 3S-4S). Secondary pulmonary hypertension, on the other hand, occurs as a result of an underlying defect or condition such as cardiac septal defects, and cirrhosis. While neointimal formation as a result of smooth muscle cell migration and proliferation resulting in a physical narrowing of the artery is characteristic of most forms of pulmonary hypertension, both primary and secondary, the diseases themselves are extremely complex and characterized by numerous symptoms. The specification defines treatment as including prophylaxis, amelioration, or cure (specification, page 10, lines 10-13). Thus the term treatment is broad and encompasses a wide variety of effects on the disease. Of these, the specification only provides enablement for inducing pulmonary vasodilation without significantly affecting systemic blood pressure or cardiac output. Based on the complex nature of hypertensive diseases, the known activities of NOS, the applicant's working examples, and the well known unpredictability of treating primary and secondary hypertension, the skilled artisan would not consider the applicant demonstration of increased vasodilation as evidence that the administration

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of NOS to the vasculature of patients would either prevent or cure the myriad of symptoms associated with hypertensive conditions.

No claims are allowed.

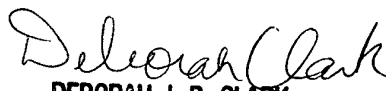
This is a CPA of applicant's earlier Application No. 08/896,053. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

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